CLINICAL PHYSIOLOGIC APPROACH TO THE PATIENT WITH PORTAL HYPERTENSION*

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In recent years new techniques of clinical investigation have been devised for the study of patients with portal hypertension; they have produced improved understanding of the physiopathology and pathogenesis of portal hypertension and a careful revision of criteria for the treatment of portal hypertension and variceal hemorrhage.

Direct catheterization of the left branch of the portal vein via the round ligament of the liver and catheterization of the coeliac trunk and of the superior mesenteric artery have permitted direct measurement of portal venous pressure;[1] determination of hepatic arterial and portal venous blood flow in unanesthetized intact man;[2-12] selective splenic, mesenteric, and portal phlebography;[13] determination in portal blood of oxygen saturation, catecholamine, and other substances;[14] coeliac and superior mesenteric arteriography;[15] injection of indicators and constant infusion of Pitressin into the superior mesenteric artery.[16]

Simultaneous catheterization of a main hepatic vein and of the left branch of the portal vein has made possible the recording both of wedged hepatic vein pressure (WHVP) and free portal vein pressure (FPVP) under physiologic conditions and with a common zero reference point: the pressure in the inferior vena cava. In large series of patients with portal cirrhosis, WHVP and FPVP have been found to be equal over a wide range of portal pressure and irrespective of the etiology and nodularity type of the cirrhosis.[1] The identity of WHVP and FPVP and the finding of a postsinusoidal type of portal hypertension in biliary cirrhosis [17, 18] where no evidence of nodular regeneration is present made it necessary to reexamine the significance of WHVP and the pathogenesis of portal hypertension in cirrhosis. By

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injection of contrast media, Reynolds and colleagues[19] demonstrated beautifully that in cirrhosis a wedged hepatic-vein catheter causes stasis in the entire hepatic vascular unit with limited runoff to the neighboring units because of damage and disconnection of the freely anastomosing sinusoidal area. The pressure of the catheter tip equals that in the portal inflow vessels. In hepatic cirrhosis the increased WHVP-FHVP gradient therefore is an expression both of increased presinusoidal and sinusoidal resistances and of post-sinusoidal resistances ("parenchymal" or "intrahepatic" type of block).

Direct catheterization of the portal vein has also stimulated the development of several methods for separate estimation of blood flow in the hepatic artery and portal vein in unanesthetized, intact man. These methods are indicator dilution techniques, methods based on the velocity of portal blood flow and estimation of the diameter of the portal vein, and methods based on the Fick principle.[2-12] By the use of electromagnetic flowmeters and by application of the methods requiring catheterization of the umbilico-portal vein it has been shown that in cirrhosis portal flow is always reduced, both in absolute value and as a fraction of total hepatic blood flow (from 60 to 70% to 40 to 50%). In about 10% of patients with cirrhosis, portal flow is markedly reduced; sometimes it is even reversed.

By a myogenic effect the decrease in portal flow elicits an increase in hepatic arterial flow; after portocaval anastomosis this flow may increase from 50 to 100% above basal values.[20]

The ratio between hepatic arterial and portal venous fraction of total hepatic blood flow is also altered or reversed in diseases which affect the radicles of the portal vein and are complicated by portal hypertension caused by presinusoidal block. In schistosomiasis and obliterative portal venopathy a perisinusoidal and a perivenous fibrosis appears over many months or years and a postsinusoidal intrahepatic increased resistance develops.[21, 22]

The increased hepatic blood flow that is produced by an arteriovenous fistula does not induce immediate portal hypertension. Increase in portal pressure is a late feature and appears as fibrosis of the liver occurs; at a late stage of the process even surgical correction of the fistula may prove ineffective.[23] All these conditions have in common an arterialization of hepatic inflow followed by fibrosis of the liver and development of increased presinusoidal or intrahepatic resistance.

A problem for the pathologist is why presinusoidal fibrosis, as described by Kluge and colleagues,[27] leads to a presinusoidal block, while in experimental and clinical portal arterialization an intrahepatic block may be also observed. Alternatively, a working postulate has been proposed which points to functional constriction of venous outflow from the hepatic sinusoids. In cirrhosis the catecholamine content of portal blood and of urine has been found to be within the normal range.[14]

In principle, portal hypertension may arise either from increase in hepatic blood flow or from increased resistance to the outflow of blood from the liver. Observation of transilluminated liver sinusoids indicates that in the fasting state only about one fifth of the sinusoids convey blood at a given time; additional sinusoids open to accommodate increased flow. Thus, even a twofold rise in flow through the liver is associated with only minor changes in portal pressure.[24]

In portal hypertension, portal pressure is usually higher than 20 mm. Hg and therefore is secondary to increased resistance to outflow. Portal hypertension may arise from thrombosis of the portal vein (extrahepatic portal hypertension) or partial occlusion of the hepatic veins (Budd-Chiari syndrome), but the most frequent cause (80 to 90%) is intrahepatic block (intrahepatic portal hypertension). The existence of an intrahepatic level of increased resistance may be deduced from histopathology, injection of vessels, corrosion studies, serial portography, cineradiography, and estimation of hemodynamic parameters. In a noncirrhotic liver an increased FPVP-WHVP gradient is a functional expression of a presinusoidal or sinusoidal block or both, and an increased WHVP-FHVP gradient of postsinusoidal block. Similarly, in a cirrhotic liver the increased WHVP-FHVP gradient derives either from a presinusoidal, sinusoidal, or postsinusoidal block.

On the basis of this information the following classification of intrahepatic portal hypertension is proposed:

Intrahepatic Portal Hypertension

Postsinusoidal block

1) Veno-occlusive disease[25]
   a) Alkaloids, plant toxins
   b) Cytotoxic drugs, e.g., urethane
   c) Radiation
2) Alcoholic hepatitis[26]

3) Partial nodular transformation[25]

Intrahepatic (parenchymal) block

1) Portal cirrhosis[25]
2) Biliary cirrhosis[17, 18]
3) Wilson's disease[25]

Presinusoidal and sinusoidal block

1) Sinusoidal portal hypertension[27]
2) Steatosis[28]
3) Idiopathic tropical splenomegaly[29]
4) Infiltrative diseases[25]
5) Obliterative portal venopathy[30, 31]
   a) Hepatoportal sclerosis
   b) Noncirrhotic portal fibrosis
   c) Idiopathic presinusoidal portal hypertension
   d) Arsenic, vynil chloride
6) Congenital hepatic fibrosis[32]
7) Schistosomiasis[21]
8) Tumors[25]
9) Acute viral hepatitis[33]

Direct catheterization of the portal vein via the round ligament of the liver and catheterization of the coeliac trunk and of the superior mesenteric artery have also yielded true progress in the diagnosis and in the clinical study of patients with portal hypertension. Umbilicoportal catheterization makes possible portal hepatography in splenectomized patients who bleed and in patients whose splenic vein is thrombosed. It may be helpful to physicians and surgeons in their decision as to the most effective type of portal-systemic shunt because it can confirm or disprove an occlusion of the portal vein suggested by splenoportography. In patients with portal hypertension caused by thrombosis of the splenic vein, umbilicoportography may visualize a patent portal vein and suggest the usefulness of splenectomy.[14] Arteriography of the hepatic and of the splenic artery is necessary for the demonstration of arteriovenous fistulas; arteriography of the superior mesenteric artery is indicated in patients who have postsplenectomy bleeding and in patients with splenoportographic exclusion of the portal vein. In extrahepatic portal hypertension (thrombosis of the portal or splenic vein) the superior mesenteric venous system is visualized and the possibility of a shunt between the mesenteric vein and the inferior vena cava can be

checked.[15] Superior mesenteric arteriography is also useful in the differential diagnosis of hemorrhage from the upper digestive tract and may be followed by continuous infusion of Pitressin or Octapressin directly into the mesenteric artery.[16]

In recent years increasing interest has been focused on the problem of a more rational selection of candidates for surgical shunt. It has become increasingly clear that liver-function tests and clinical examination do not permit prediction of survival or encephalopathy.[34] There is evidence that diversion of portal blood from the liver influences hepatic function and therefore survival; patients who have normal or increased portal flow may not tolerate a portocaval shunt.[35] In randomly selected patients with cirrhosis, those who exhibit spontaneous reversal of portal flow have the lowest survival rate.[36]

The development of reliable methods for preoperative determination of portal flow in intact patients now makes it possible to test this hypothesis by prospective, controlled studies in a large series. Such studies are badly needed.

Multicentric prospective controlled studies are also needed for determination of the survival rate and the incidence of encephalopathy in cirrhotics who undergo distal or selective shunt, or end-to-side portocaval shunt with arterialization of the distal stump of the portal vein. These new types of portal-systemic shunts have been developed both to reduce tension in the area critical for hemorrhage and to preserve a large nutritional blood flow to the liver, avoiding the dramatic negative change found in patients who have high portal inflow before operation.[34, 37-42]

Another urgent task is the critical evaluation, by prospective controlled trials, of the medical management of bleeding esophageal varices. Efforts should be made to give bleeding patients the opportunity of rational diagnosis and treatment in an intensive-care unit by a highly specialized team, including an experienced gastroenterologist, an endoscopist, a radiologist, and a surgeon. This would give all the patients a common bias and would represent the basal condition for critical evaluation of the ingenious forms of therapy that have been developed recently.

A very high survival rate has been reported after continuous and careful use of a modified Sengstaken-Blackemore tube and impressive results have been obtained by continuous infusion of vasopressin or

Octapressin into the superior mesenteric artery.[16, 43] The results obtained with these conservative forms of treatment should be compared prospectively with the survival after emergency portocaval anastomosis.

In discussing the pathological physiology and the treatment of portal hypertension I have undertaken to present some of the main problems that are encountered in connection with the new techniques of clinical investigation. The problems are of interest to the pathologist, the gastroenterologist, and the surgeon, hence their collaboration is highly desirable. In particular, multicentric clinical trials are greatly needed in order to establish the real value of the various medical and surgical therapeutic approaches that have been recently proposed and advocated. I suggest that they might be promoted by the International Association for Study of the Liver on a multinational base, prompting a large cooperative international effort.

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A paper presented at *A Day on the Liver* by Ian R. Mackay, M.D., "The Concept of Autoimmune Liver Disease," was received too late for publication in this issue. It will appear in a future issue of the *Bulletin.*

ERRATUM

In the March 1975 issue, page 447, Appendix B should have included the names of Drs. Robert H. Felix (1963) and Harry C. Solomon (1969). Contrary to a statement which appears on page 445, the Salmon Medal does not bear the name of the American Psychiatric Association. The Salmon Committee on Psychiatry and Mental Hygiene is appointed by the New York Academy of Medicine.